BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

AMENDMENT TO THE SPECIFICATION

On page 6, please replace the third full paragraph with the rewritten paragraph provided herewith.

--In a tenth aspect, the invention provides a method for increasing the immunostimulatory effect of a CpG-containing oligonucleotide. The method according to this aspect of the invention comprises introducing into the oligonucleotide a 3' substituted nucleoside at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, ~~2 nucleosides~~ 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and combinations thereof. In certain preferred embodiments, the oligonucleotide is not an antisense oligonucleotide. In preferred embodiments, this method includes creating a 2'-5' linkage between the 2' position of a 3' substituted nucleoside and the 5' position of another nucleoside, which may or may not be a 3' substituted nucleoside.--

At the bottom of page 6 going over to page 7, please replace the paragraph traversing these pages with the following rewritten paragraph.

-- In a eleventh aspect, the invention provides CpG-containing oligonucleotides having increased immunostimulatory effects, the oligonucleotide comprising a 3' substituted nucleoside at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, ~~2 nucleosides~~ 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3'

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and combinations thereof. In certain embodiments, the oligonucleotide is not an antisense oligonucleotide. . In preferred embodiments, CpG-containing oligonucleotides according to this aspect of the invention include a 2'-5' linkage between the 2' position of a 3' substituted nucleoside and the 5' position of another nucleoside, which may or may not be a 3' substituted nucleoside.--

On page 7, replace the first full paragraph with the following rewritten paragraph.

-- In an twelfth aspect, the invention provides a method for inducing an immune response in a mammal, the method comprising administering to the mammal an oligonucleotide comprising a 3'-substituted nucleoside at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, ~~2 nucleosides~~ 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and combinations thereof. In certain preferred embodiments, the oligonucleotide is not an antisense oligonucleotide. In preferred embodiments, CpG-containing oligonucleotides used in this aspect of the invention include a 2'-5' linkage between the 2' position of a 3' substituted nucleoside and the 5' position of another nucleoside, which may or may not be a 3' substituted nucleoside. --

On page 7 going onto page 8, please replace the paragraph that traverses these two pages with the following rewritten paragraph.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

--In a thirteenth aspect, the invention provides a method for increasing the immunostimulatory effect of a CpG-containing oligonucleotide. The method according to this aspect of the invention comprises introducing into the oligonucleotide an uncharged internucleoside linkage at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, ~~2 nucleosides~~ 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and combinations thereof. In certain preferred embodiments, the oligonucleotide is not an antisense oligonucleotide. --

On page 8, please replace the first full paragraph with the following rewritten paragraph.

-- In a fourteenth aspect, the invention provides CpG-containing oligonucleotides having increased immunostimulatory effects, the oligonucleotide comprising an uncharged internucleoside at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, ~~2~~ ~~nucleosides~~ 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and combinations thereof. --

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

On page 8 going onto page 9, please replace the paragraph that traverses these two pages with the following rewritten paragraph.

-- In a fifteenth aspect, the invention provides a method for inducing an immune response in a mammal, the method comprising administering to the mammal an oligonucleotide comprising an uncharged internucleoside linkage at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, ~~2 nucleosides~~ 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and combinations thereof. In certain preferred embodiments, the oligonucleotide is not an antisense oligonucleotide. --

On page 9, please replace the first full paragraph with the following rewritten paragraph.

-- In a sixteenth aspect, the invention provides a method for increasing the immunostimulatory effect of a CpG-containing oligonucleotide. The method according to this aspect of the invention comprises introducing into the oligonucleotide a 2'-5' internucleoside linkage at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, ~~2~~ ~~nucleosides~~ 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

combinations thereof. In certain preferred embodiments, the oligonucleotide is not an antisense oligonucleotide. --

On page 9, please replace the last paragraph with the following rewritten paragraph.

-- In a seventeenth aspect, the invention provides CpG-containing oligonucleotides having increased immunostimulatory effects, the oligonucleotide comprising a 2'-5' internucleoside linkage at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, ~~2 nucleosides~~ 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and combinations thereof. --

On page 10, please replace the only paragraph on this page with the following rewritten paragraph.

-- In an eighteenth aspect, the invention provides a method for inducing an immune response in a mammal, the method comprising administering to the mammal an oligonucleotide comprising a 2'-5' internucleoside linkage at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, ~~2 nucleosides~~ 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

A10 cont'd

dinucleotide, and combinations thereof. In certain preferred embodiments, the oligonucleotide is not an antisense oligonucleotide. --

On page 11, please delete the second paragraph, which provides a description of Figure 2.

On page 11, please delete the third paragraph and replace it with the following rewritten paragraph.

A11

-- Figure 2 ~~3~~ shows results of a proliferation assay of mouse spleen cells and shows spleen enlargement in mice administered no oligonucleotide (C), or various unsubstituted or methylphosphonate substituted oligonucleotides. Underlined nucleosides have a methylphosphonate linkage at the 3' position.

On page 19 going onto page 20, please replace the paragraph that traverses these two pages with the following rewritten paragraph.

A12

-- In a tenth aspect, the invention provides a method for increasing the immunostimulatory effect of a CpG-containing oligonucleotide. The method according to this aspect of the invention comprises introducing into the oligonucleotide a 3' substituted nucleoside at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, ~~2 nucleosides~~ 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and combinations thereof. In certain preferred embodiments, the oligonucleotide is not an antisense oligonucleotide. In preferred embodiments, this method includes creating a 2'-5' linkage between the 2' position of a 3' substituted nucleoside and the 5' position of another nucleoside, which may or may not be a 3' substituted nucleoside. --

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

On page 20, please replace the second full paragraph with the following rewritten paragraph.

-- The method according to this aspect of the invention can be conveniently carried out using any of the well-known synthesis techniques by simply using the appropriate 3' substituted monomer synthon in the synthesis process in the cycle immediately following the incorporation of the CpG dinucleotide. Preferred monomers include phosphoramidites, phosphotriesters and H-phosphonates. Thus, for purposes of the invention, "introducing into the oligonucleotide a 3' substituted nucleoside at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, ~~2 nucleosides~~ 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and combinations thereof." simply means synthesizing an oligonucleotide that has a 3' substituted nucleoside at such a position or positions. --

On page 20 going onto page 21, please replace the paragraph that traverses these two pages with the following rewritten paragraph.

-- In a eleventh aspect, the invention provides CpG-containing oligonucleotides having increased immunostimulatory effects, the oligonucleotide comprising a 3' substituted nucleoside at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, ~~2 nucleosides~~ 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3'

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and combinations thereof. In certain embodiments, the oligonucleotide is not an antisense oligonucleotide. In preferred embodiments, CpG-containing oligonucleotides according to this aspect of the invention include a 2'-5' linkage between the 2' position of a 3' substituted nucleoside and the 5' position of another nucleoside, which may or may not be a 3' substituted nucleoside. --

A14 cont'd

On page 21 going onto page 22, please replace the paragraph that traverses these two pages with the following rewritten paragraph.

-- In a twelfth aspect, the invention provides a method for inducing an immune response in a mammal, the method comprising administering to the mammal an oligonucleotide comprising a 3'-substituted nucleoside at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, ~~2 nucleosides~~ 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and combinations thereof. In certain preferred embodiments, the oligonucleotide is not an antisense oligonucleotide. In preferred embodiments, CpG-containing oligonucleotides used in this aspect of the invention include a 2'-5' linkage between the 2' position of a 3' substituted nucleoside and the 5' position of another nucleoside, which may or may not be a 3' substituted nucleoside. --

A15

On page 23, please replace the last full paragraph with the following rewritten paragraph.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

-- In a thirteenth aspect, the invention provides a method for increasing the immunostimulatory effect of a CpG-containing oligonucleotide. The method according to this aspect of the invention comprises introducing into the oligonucleotide an uncharged internucleoside linkage at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, ~~2 nucleosides~~ 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and combinations thereof. In certain preferred embodiments, the oligonucleotide is not an antisense oligonucleotide. --

On page 24 going onto page 25, please replace the paragraph that traverses these two pages with the following rewritten paragraph.

-- In a fourteenth aspect, the invention provides CpG-containing oligonucleotides having increased immunostimulatory effects, the oligonucleotide comprising an uncharged internucleoside at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, ~~2 nucleosides~~ 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and combinations thereof. Preferred oligonucleotides according to this aspect of the invention are complementary to a gene or gene transcript. More

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

preferably, such oligonucleotides have antisense activity. In some preferred embodiments, the oligonucleotide has only one uncharged internucleoside linkage for each CpG dinucleotide present in the oligonucleotide. In some preferred embodiments, the oligonucleotide has only one an uncharged internucleoside linkage. --

a17 cancel

On page 25, please replace the second full paragraph with the following rewritten paragraph.

-- In a fifteenth aspect, the invention provides a method for inducing an immune response in a mammal, the method comprising administering to the mammal an oligonucleotide comprising an uncharged internucleoside linkage at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and combinations thereof. In certain preferred embodiments, the oligonucleotide is not an antisense oligonucleotide. --

a18

On page 26 going on to page 27, please replace the paragraph that traverses these pages with the following rewritten paragraph.

a19

-- In a sixteenth aspect, the invention provides a method for increasing the immunostimulatory effect of a CpG-containing oligonucleotide. The method according to this aspect of the invention comprises introducing into the oligonucleotide a 2'-5' internucleoside linkage at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, 2nd

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and combinations thereof. In certain preferred embodiments, the oligonucleotide is not an antisense oligonucleotide. --

Q19 cancel

On page 27 going on to page 28, please replace the paragraph that traverses these pages with the following rewritten paragraph.

-- In a seventeenth aspect, the invention provides CpG-containing oligonucleotides having increased immunostimulatory effects, the oligonucleotide comprising a 2'-5' internucleoside linkage at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to the CpG dinucleotide, 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and combinations thereof. --

Q20

On page 28, please replace the second full paragraph with the following rewritten [paragraph.]

-- In an eighteenth aspect, the invention provides a method for inducing an immune response in a mammal, the method comprising administering to the mammal an oligonucleotide comprising a 2'-5' internucleoside linkage at a position selected from the group consisting of 3rd nucleoside 5' to the CpG dinucleotide, 4th nucleoside 5' to the CpG dinucleotide, 5th nucleoside 5' to the CpG dinucleotide, 6th nucleoside 5' to

Q21

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

the CpG dinucleotide, 2nd nucleoside 3' to the CpG dinucleotide, 3rd nucleoside 3' to the CpG dinucleotide, 4th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 5th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 6th nucleoside 3' to the CpG dinucleotide, ~~5th~~ 7th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 8th nucleoside 3' to the CpG dinucleotide, ~~6th~~ 9th nucleoside 3' to the CpG dinucleotide, ~~4th~~ 10th nucleoside 3' to the CpG dinucleotide, and combinations thereof. In certain preferred embodiments, the oligonucleotide is not an antisense oligonucleotide. --

On page ~~32~~ 31, please replace the first paragraph under Example 2 with the following rewritten paragraph.

-- To evaluate the immunostimulatory activity of oligonucleotides in the present study, ~~we have used~~ a mouse spleen cell proliferation assay in which mouse spleen cells were cultured with oligonucleotide at concentrations of 0.1, 1.0 and 10 μg/ml. ~~, as described in Example 1.~~ The oligos shown in Table 1 were used for these studies. --

On page 32, please replace the first full paragraph with the following rewritten paragraph.

-- We used a PS-oligonucleotide containing a single CpG dinucleotide (Oligo 1) and Oligos 2-5 in which substitution of one deoxynucleoside ~~or two deoxynucleosides~~ was carried out with modified nucleosides at specific sites. Results are presented in Figure 1. --

On page 32, please replace the second full paragraph with the following rewritten paragraph.

-- Substitution with 3'-O-methyl ribonucleosides in Oligos 2.5 simultaneously led to incorporation of 2'-5' internucleoside linkages. Substitution 5' of the CpG dinucleotide with no intervening nucleosides (Oligo 2) diminished immunostimulatory activity. Surprisingly, substitution 3' of the CpG dinucleotide with no intervening nucleosides (Oligo 5) also diminished immunostimulatory activity. In addition, Oligos 3 and 4, with 3'-O-methylribonucleoside substitution ~~3'~~ 5' to the CpG dinucleotide increase

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

A24 cont'd

immunostimulatory activity (indices of 4.6 +/- 0.43 and 5.7 +/- 0.87, respectively. --

On page 32, please replace the third full paragraph with the following rewritten paragraph.

A25

-- Oligonucleotides containing methylphosphonate internucleotide linkages are shown in Figure ~~3~~ 2. Oligonucleotides were prepared having methylphosphonate linkages 3 or 4 nucleotides 5' to the CpG dinucleotide, or 2 or 3 nucleotides 3' to the CpG dinucleotide. As shown in Figure ~~3~~ 2, all of these oligonucleotides were more immunostimulatory than Oligo **1** in both the mouse spleen cell proliferation assay and the spleen enlargement assay. --